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Regioselective Synthesis of Medium-Sized Bicyclic Butenolides by Lewis Acid Catalyzed Cyclization of Cyclic 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Oxalyl Chloride

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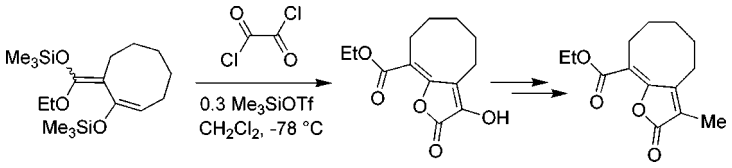
ABSTRACT



A new strategy for the synthesis of medium-sized bicyclic γ-alkylidenebutenolides is reported which involves Me_3SiOTf-catalyzed cyclization of cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride.

Many natural products, including prominent compounds such as freelingyne, tetrenolin, dihydroxerulin and patulin, belong to the pharmacologically important group of γ-alkylidenebutenolides.[1,2] Among this group, medium-sized bicyclic butenolides are found in a variety of biologically active natural products: the large genus *Vernonia* includes the germacranolides,[3] cytotoxic lactone analogues of the sesquiterpene ketone germacrone, and the highly oxygenated hirsutinolides and glaucolides which include a number of antibiotically active compounds.[4] The substance class of the tagitinins also includes several natural products such as ciliarin, zexbrevin, tagitinin A, or calaxin.[5] We have recently reported a new synthesis of α-hydroxy-γ-alkylidenebutenolides by the first regio- and stereoselective cyclizations of 1,3-dicarbonyl dianion equivalents with oxalic acid dielectrophiles.[6] Herein, we wish to report an efficient synthesis of 5,*n*-bicyclic butenolides ($n = 5-12$) which represent

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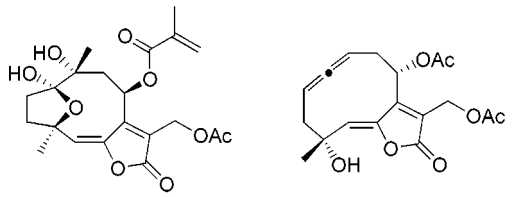
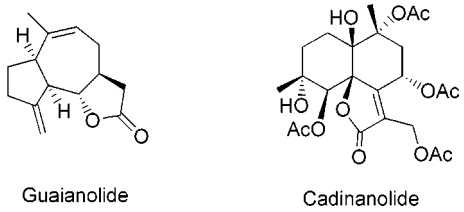
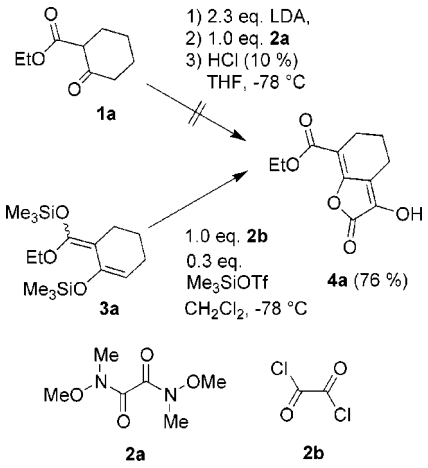
analogues of pharmacologically relevant sesquiterpene natural products.





Our initial attempts to apply our dianion methodology to cyclic substrates failed.[6c] Reaction of the dianion of ethyl cyclohexanone-2-carboxylate **1a** (generated by means of 2 equiv of LDA) with *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide **2a**, the Weinreb amide of oxalic acid,[6a] resulted in the formation of a complex mixture rather than the desired butenolide **4a** (Scheme 1). Therefore, we have envisaged a

Scheme 1

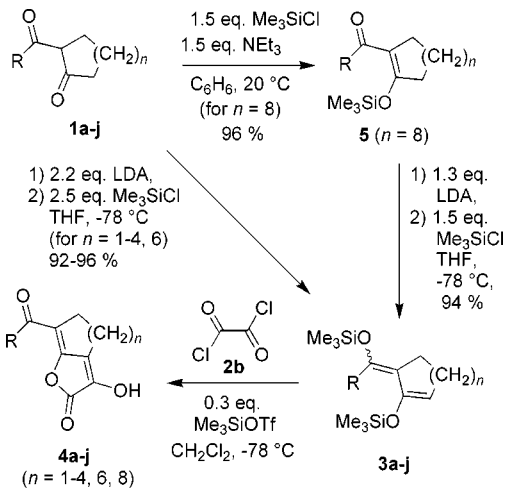


Lewis acid-catalyzed synthesis of butenolide **4a** via the 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a** which represents an electroneutral dianion equivalent.[6c,7]

Our starting point was the synthesis of the known β-keto esters **1h**−**j** by NaH-mediated reaction of dimethyl or diethyl carbonate with the corresponding cyclic ketones. The 1,3-diketones **1d** and **1g** were prepared by reaction of the respective ketone enolates (which were formed by LDA) with benzoyl and pivaloyl chloride. The 12-membered cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3j** was prepared in two steps as described for the synthesis of open-chain dienes:[7d] silylation of the 1,3-dicarbonyl compound **1j** afforded the silyl enol ether **5** (96% yield) which was transformed in high yield into the 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3j** by treatment with LDA at −78 °C and subsequent addition of Me_3SiCl. Inseparable mixtures were obtained when this protocol was applied to 1,3-dicarbonyl compounds of smaller ring size. However, these compounds could be prepared by a known one-step synthesis:[7d,8] the dianions of **1a**−**i** were generated by treatment of the 1,3-dicarbonyl compounds with 2 equiv of LDA. Addition of Me_3SiCl, stirring for 2 h at 0 °C and subsequent nonaquoeus workup afforded the 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3a**−**d** and **3f**−**i** in high yields.[7d] In the five-membered ring case, a 2:1 mixture of **3e** and of a monosilyl enol ether was obtained. The reaction of Me_3SiCl with dianions of *open-chain* β-keto esters has been reported to result in significant silylation of the terminal carbon atom of the dianion.[7b]

With dienes **3a**−**j** in hands, the synthesis of bicyclic γ-alkylidenebutenolides was studied. The Me_3SiOTf-catalyzed cyclization of oxalyl chloride **2b** with the ethyl cyclohexanone-2-carboxylate derived 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a** afforded the γ-alkylidenebutenolide **4a** in 76% yield (Scheme 1).[6c,9] To study the preparative scope of our methodology for the synthesis of bicyclic γ-alkylidenebutenolides, the ring size and the substituents of the 1,3-bis(trimethylsilyloxy)-1,3-butadienes were systematically varied (Scheme 2, Table 1). The reaction of

Scheme 2



oxalyl chloride with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3b**−**i** afforded the respective 5,5-, 5,6-, 5,7-, 5,8- and 5,10-bicyclic γ-alkylidenebutenolides **4b**−**i** in good yields. All reactions proceeded regioselectively by initial attack of

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Table 1

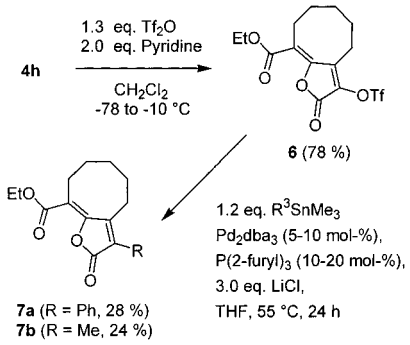
4	R	*n*	yield [%] [a]
a	OCH_2CH_3	2	76
b	$OCH(CH_3)_2$	2	74
c	$OCH_2CH_2OCH_3$	2	75
d	C_6H_5	2	68
e	OCH_2CH_3	1	55
f	OCH_2CH_3	3	84
g	$C(CH_3)_3$	3	75
h	OCH_2CH_3	4	74
i	OCH_3	6	73
j	OCH_3	8	70

[a] Isolated yield. For butenolides **4a**−**i**, only one geometric isomer was formed. Butenolide **4j** was obtained as a mixture of isomers (*E*:*Z* = 1:4).

the terminal (rather than the central) carbon atom of the diene onto the dielectrophile and subsequent cyclization via the neighboring oxygen atom. Starting with the 10-membered ring diene **3i**, the *Z*-configured butenolide **4i** was formed with excellent stereoselectivity. The respective *E*-configured product was not formed. Cyclization of oxalyl chloride with bis-silyl enol ether **3j** resulted in formation of the 5,12-bicyclic butenolide **4j** which was obtained as a 4:1 mixture of geometric isomers (*E*:*Z* = 1:4).

To demonstrate the synthetic usefulness of our methodology, we studied the functionalization of the α-carbon of the medium-sized bicyclic butenolides by palladium-catalyzed cross-coupling reactions. The 5,8-bicyclic butenolide **4h** was transformed by trifluoromethanesulfonic anhydride/ pyridine into the corresponding triflate **6** (Scheme 3).

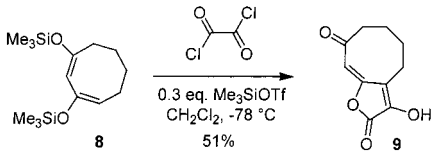
Scheme 3



Optimal yields were obtained for Stille reactions of triflate **6** when $Pd_2dba_3{\cdot}CHCl_3$ (5−10 mol %), LiCl (3 equiv), and P(2-furyl)$_3$ (10−20 mol %) were used.[10,11] Reaction of **6** with trimethylphenylstannane and tetramethylstannane afforded the γ-alkylidenebutenolides **7a**,**b**.

The applicability of our cyclization reaction to medium-sized rings containing a different substitution pattern was next studied: the eight-membered cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadiene **8** was prepared from cyclooctan-1,3-dione in one step. To our satisfaction, the Me_3SiOTf-catalyzed cyclization of **8** with oxalyl chloride proceeded uneventfully and afforded the *E*-configured 5,8-bicyclic butenolide **9** in acceptable yield and with very good regioselectivity (Scheme 4).

Scheme 4



In summary, we have developed a new and efficient synthesis of bicyclic γ-alkylidenebutenolides containing 5−12-membered rings annulated to the butenolide moiety. The products were prepared in good yields from readily available starting materials. The medium-sized bicyclic butenolides represent analogues of a variety of pharmacologically relevant natural products.

(8) **Representative experimental procedure:** To a THF solution (30 mL) of LDA, prepared by addition of *n*-BuLi (20.91 mL, 32 mmol, solution in *n*-hexane) to a THF solution of diisopropylamine (3.67 mL, 32 mmol) was added dropwise ethyl cycloheptanone-2-carboxylate (**1f**) (2.69 g, 14.6 mmol) at 0 °C. After stirring of the yellow solution for 1.5 h at 0 °C, trimethylchlorosilane (5.5 mL, 43.8 mmol) was added in one portion. After stirring for 2 h at 0 °C, the solvent was removed in vacuo. To the residue was added petroleum ether, and the suspension obtained was filtered. The solvent of the filtrate was removed in vacuo to give essentially pure 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3f** in 95% crude yield. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.10, 0.21 (2 × s, 2 × 9 H, Me_3Si), 1.22 (t, *J* = 7 Hz, 3 H, CH_3), 1.45−1.65 (2 × m, 2 × H, CH_2), 1.95, 2.18 (2 *x* m, 2 × 2 H, CH_2), 3.82 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 4.94 (t, *J* = 6.5 Hz, 1 H, OH). All new compounds were characterized spectroscopically and gave correct elemental analyses and/or high-resolution mass spectra.

(9) **Representative experimental procedure:** To a CH_2Cl_2 solution (60 mL) of oxalyl chloride (3.94 mmol, 0.34 mL) and 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3f** (3.28 mmol, 1.08 g) was added a CH_2Cl_2 solution (7 mL) of Me_3SiOTf (0.18 mL, 0.3 equiv) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After stirring for 2 h at 20 °C, a saturated solution of NaCl was added, the organic layer was separated, and the aqueous layer was repeatedly extracted with ether. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, ether/petroleum ether = 1:10 → 1:1) to give **4f** (781 mg, 84%) as a colorless solid, mp 78 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.28 (t, *J* = 6 Hz, 3 H, CH_3), 1.65−1.90 (m, 4 H, CH_2), 2.64 (m, 4 H, CH_2), 4.25 (q, *J* = 6 Hz, 2 H, OCH_2CH_3), 8.00 (br, 1 H, OH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 13.91 (CH_3), 23.88, 24.01, 26.59, 28.53 (CH_2), 61.55 (OCH_2CH_3), 117.21, 126.85, 141.60, 148.68, 164.82, 167.18 (C). MS (EI, 70 eV): 238 (M^+, 100). Anal. Calcd for $C_{12}H_{14}O_5$: C 60.50, H 5.92. Found: C 60.28, H 5.75.

(10) **Representative experimental procedure:** To a THF solution (5 mL) of triflate **6** (0.46 mmol, 176 mg) were added $Pd_2dba_3{\cdot}CHCl_3$ (10 mol %, 48 mg), P(2-furyl)$_3$ (20 mol %, 43 mg), and LiCl (1.38 mmol, 59 mg). After stirring for 5 min, tetramethylstannane (0.55 mmol, 0.080 mL) was added. After stirring for 24 h at 55 °C, water (100 mL) was added. The aqueous layer was extracted with ether (4 × 100 mL), the organic layer was dried ($MgSO_4$) and filtrated, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography.

(11) For the first use of Pd_2dba_3 and P(2-furyl)$_3$ in Stille reactions, see: Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino Jr., C. *J. Org. Chem.* **1990**, *55*, 5833.

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Supporting Information Available: Procedures for the preparation and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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